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CLEARING THE SMOKE:

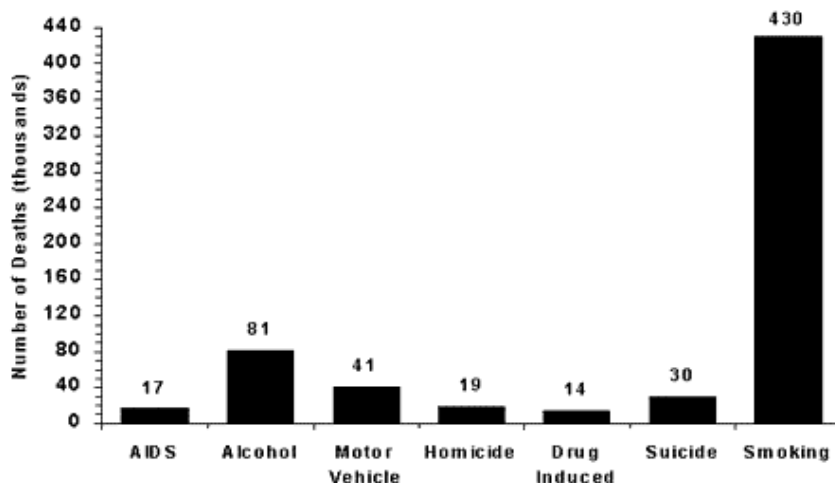
ASSESSING THE SCIENCE BASE FOR TOBACCO HARM REDUCTION

Tobacco use, especially cigarette smoking, is the single largest environmental cause of death and disease in the United States. Claiming more than 400,000 lives annually, smoking kills more people than do AIDS, alcohol, cocaine, heroin, homicide, suicide, motor vehicle crashes, and fires combined. The primary causes of death from tobacco each year are cardiovascular disease (approximately 180,000 deaths), cancer (approximately 150,000 deaths), and respiratory disease (approximately 85,000 deaths). The average reduction in life expectancy for smokers is 6.6 years.

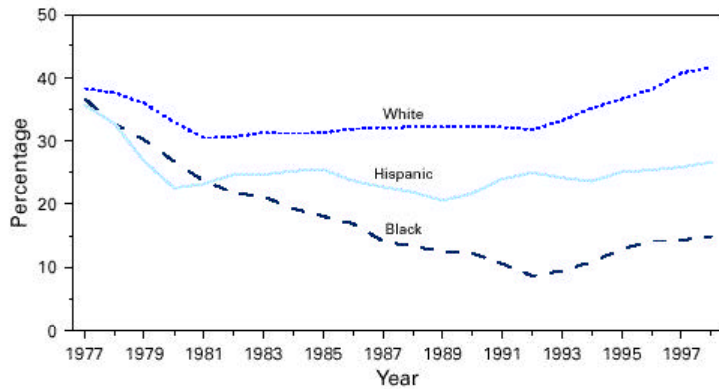
Even nonsmokers are threatened, facing exposure to the “environmental tobacco smoke” produced by smokers, as well as to other hazardous situations, especially fires, that arise from smoking. For example, approximately 30,000 nonsmokers die each year from cardiovascular disease caused by the inhalation of second-hand smoke. Also, the maternal and paternal smoker places the fetus and infant at risk for numerous growth and developmental impairments.

The dangers of smoking have been known for decades. Among the major early warnings, the first U.S. Surgeon General’s report on smoking and health, issued in 1964, concluded that “the use of tobacco, especially cigarette smoking, has been causally linked to several diseases,” including lung cancer, coronary artery disease, chronic bronchitis, and emphysema.

Yet today, roughly 48 million adults—nearly one-quarter of the adult population—smoke cigarettes. Although this rate is far lower than the 42 percent recorded in 1965, the decline in smoking among adults appears to have leveled off during much of the past decade. Many adolescents also are smoking regularly or are experimenting with tobacco use. In a recent survey, nearly 13 percent of middle-school students and 35 percent of high-school students reported smoking during the preceding month—a troubling



Comparative causes of annual deaths in the United States. SOURCE: CDC.



Trends in cigarette smoking* among 12th graders, by racial/ethnic group—United States, 1977–1998.[†]

*Smoking on □ 1 of the 30 days before the survey. [†]2-year moving averages are used to stabilize estimates.

SOURCE: CDC/University of Michigan, Monitoring the Future Project.

Thus, while 70 percent of smokers say they want to quit, and 34 percent of smokers attempt to quit each year, only 10 percent of those who try to quit actually break their addiction and remain tobacco-free for a year.

Numerous products that make explicit or implied claims to lower the health risks of cigarettes and other forms of tobacco have been introduced into the U.S. marketplace—and there is a strong likelihood of more products and increased marketing in the near future.

finding given that the vast majority of adult smokers begin during their youth.

A Role for Harm Reduction

Without doubt, the best way for people to avoid the health risks of smoking is to never begin smoking, and the best way for those who already smoke to minimize their health risks is to quit promptly. Even after years of smoking, quitting reduces risk both immediately and in the long-term for many tobacco-related conditions. Several types of smoking cessation programs, some aimed at individuals and some at communities, have been shown to

be modestly effective. For many smokers, however, quitting proves difficult. The simple fact is tobacco contains nicotine, which is both pleasurable to the user and highly addictive. Thus, while 70 percent of smokers say they want to quit, and 34 percent of smokers attempt to quit each year, only 10 percent of those who try to quit actually break their addiction and remain tobacco-free for a year.

Because many people cannot or will not stop using tobacco, and because many adolescents will continue to experiment with things “taboo,” there almost certainly will remain a significant population whose health is at risk from smoking. Indeed, it has been predicted that even with the most intensive application of the most effective programs for abstinence and cessation, at least 10 percent to 15 percent of adults in the United States would continue to smoke.

The huge personal and public toll of smoking has prompted the search for means to reduce the harm associated with tobacco use for those individuals who continue to smoke. Numerous products that make explicit or implied claims to lower the health risks of cigarettes and other forms of tobacco have been introduced into the U.S. marketplace—and there is a strong likelihood of more products and increased marketing in the near future.

In light of such developments, the U.S. Food and Drug Administration asked the Institute of Medicine, an arm of the National Academy of Sciences, to convene a committee of experts to lay out the scientific methods and standards by which these products and their effect on public health could be assessed. The committee issued its report, called *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction*, in February 2001.

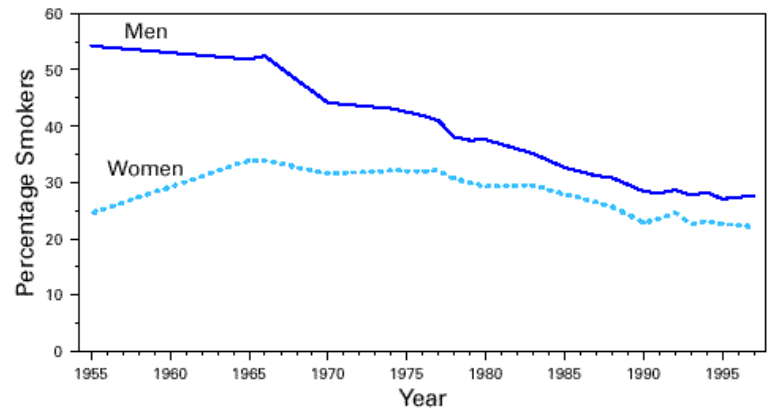
Products Aimed at Risk Reduction

The committee focused on two types of products, both of which are intended to reduce tobacco-related exposure and potentially reduce the risk of disease compared to conventional tobacco products.

The first type includes tobacco and cigarette-like products that result in potentially decreased emission of some toxicants. Some of these products are made with different types of tobacco or additives, or they are made using different methods of curing, blending, or processing the tobacco. Others use modified delivery systems that change the composition of the smoke that the user inhales by such means as reducing the burning temperature of the tobacco, diluting the smoke with air, or adding special “carriers” for smoke particles.

The second type includes several pharmaceutical agents, some of which are currently approved for short-term use in smoking cessation. These products might be used long-term to maintain cessation or concomitantly with continued but decreased consumption of cigarettes or other conventional forms of tobacco. Many of these products contain nicotine incorporated into patches, gums, oral inhalers, and nasal sprays. Others contain particular antidepressants that reduce the craving for tobacco.

Although both types of products could potentially result in *reduced exposure* to toxicants from a given instance of tobacco use, such reduced exposure does not necessarily assure *reduced risk* to the individual user or *reduced harm* to the larger population. At the population level, for example, the potential benefits might be reduced if some people, perceiving these products to be safer, begin using tobacco who otherwise would not have done so, if some smokers who might have quit do not, or if some former smokers resume smoking. Therefore, and in order to avoid any misinterpretation, the committee chose to use the generic term “potential reduced-exposure products,” or PREPs, to describe these products. Despite any potential harm reduction that PREPs may offer, the use of tobacco in any form poses greater risk than having no exposure to tobacco at all.



Trends in cigarette smoking* among persons aged 18 years, by sex—United States, 1955–1997.
SOURCE: CDC/1955 Current Population Survey; 1965–1997 National Health Review Survey.

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What We Know

In considering these products, the committee examined four basic questions: (1) Does use of a product decrease exposure to the harmful substances in tobacco? (2) Is this decreased exposure associated with decreased harm to health? (3) Since actual health effects associated with these products might not appear for many years, are there surrogate indicators of their effects that could be measured in a time frame sufficient for product evaluation? (4) What are the public health implications of tobacco harm-reduction products? Where answers could not be determined, the committee was asked to propose a broad strategy by which the knowledge base should be assembled.

The committee reached the following principal conclusions regarding these questions:

- There are sufficient data to suggest that, for many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is biologically and clinically feasible.
- No PREPs have yet been evaluated comprehensively enough (including for a sufficient time) to provide evidence for concluding that they are associated with a reduced risk of disease compared to conventional tobacco use. Such impact likely will not be directly or conclusively demonstrated for many years.
- Surrogate measures of tobacco-related diseases exist that could be used to give guidance or to help predict whether or not PREPs are likely to be risk-reducing. Available candidate surrogate measures must be further validated and more must be developed in order to be useful for PREP evaluation and regulation.
- PREPs exist that have been or could be demonstrated to reduce exposure to some of the toxicants in most conventional tobacco products.
- Regulation of all tobacco products (as recommended in the 1994 IOM report *Growing up Tobacco Free: Preventing Nicotine Addiction in Children and Youths*), including all PREPs, is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected. Regulation could assure that adequate research, on everything from smoke chemistry and toxicology to long-term epidemiology, is conducted and that the public receives reliable information as to the risks and benefits of PREPs.
- The public health impact of PREPs is unknown. They are potentially beneficial, but the net impact on population health could, in fact, be negative.

A Comprehensive Approach to Tobacco Harm Reduction

...tobacco harm reductions efforts... necessarily rely on public health tools such as research, surveillance, and regulation aimed at improving education and communication directed to the consumer.

Following on these general conclusions, tobacco harm reduction efforts, if conducted properly, could lead to reduced tobacco-related morbidity and mortality for those people who cannot or will not give up tobacco. Such an effort necessarily relies on public health tools such as research, surveillance, and regulation aimed at improving education and communication directed to the consumer.

Research

In order to strengthen the evidence base for harm reduction, the committee presented a more specific research agenda for assessing harm-reduction products. The plan identified five general scientific areas that should be explored:

1. *Description of the dose-response relationship between tobacco smoke and/or constituent exposure and health outcomes.* There are more than 4,000 different chemicals in tobacco smoke, many of them toxic. For the most part, the data are insufficient to accurately describe the relationship of tobacco use and disease formation at the level of detail that would establish all casual agents or the exact dose-response relationship. Consequently, the confidence with which the potential benefits or risks of PREPs can be extrapolated, especially at low doses,

is uncertain.

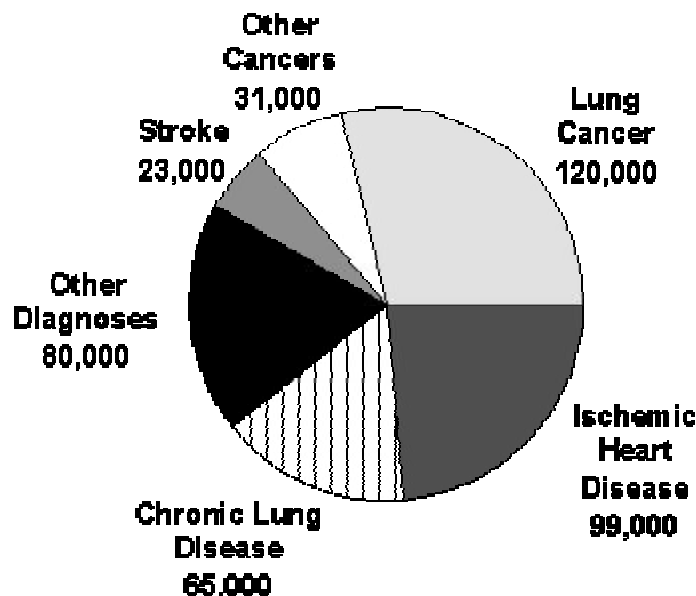
2. *Identification and development of surrogate markers for disease.* Possible markers include, for example, measures of inflammation and vascular activation, which may be related to measures of cardiovascular physiology and, ultimately, reflect the risk of clinical cardiovascular disease or lung disease. Biomarkers of genetic damage in blood, sputum, urine, and internal organs may indicate early carcinogenic processes and risk of cancer development. Ideally, a set of behavioral markers also might be developed to monitor such things as the substitution of PREPs for smoking cessation or the increase in initiation due to the availability of PREPs.

3. *Preclinical research.* Animal models and in vitro testing can contribute to the design and evaluation of PREPs. In particular, the new technologies of genomics and proteomics have great potential for evaluating and comparing the effects of tobacco exposure and use of PREPs on gene translation and expression in cancerous and noncancerous diseases.

4. *Short-term clinical and epidemiological studies.* Some effects of PREPs could be detected by epidemiological studies, by measurement of intermediate disease markers, or by clinical studies of smokers who are unwilling or unable to quit but are willing to use PREPs compared to a control group of users of conventional tobacco products. Validated biomarkers of disease, when available, should be developed in these studies in order to assess potential risk reduction within a practical time-frame. Human studies also are required for evaluating the relationship of such various factors as individual smoking history, environment, gender, race, and diet to disease risk and likelihood of harm reduction.

5. *The role of long-term epidemiological studies and surveillance.* Most tobacco-related diseases develop clinically over several years. Thus, the only direct and definitive way to assess the value of PREPs is to monitor the health outcomes of users compared to control groups over an extended period.

To help in organizing the scientific base for evaluation of PREPs, the committee made use of a risk assessment framework similar to that used to gauge the health risks for other environmental and occupational exposures. In particular, the committee turned to a 1983 National Research Council report called *Risk Assessment in the Federal Government*. Known as “The Red Book,” the report outlined several basic steps in risk assessment. These steps include hazard identification (Does the toxicant cause the adverse effect?), dose-response assessment (What is the relationship between toxicant dose and disease incidence in humans?), exposure assessment (What exposures are currently experienced or anticipated under different circumstances?), and risk characterization (What is the estimated incidence of the adverse effect in a given population?). The process also must take into account public health, social, economic, and political considerations.



Deaths attributable to Cigarette Smoking—United States, 1990.
SOURCE: CDC SAMMEC, MMWR 1993; 42:645–9.

Only a comprehensive program of surveillance and regulation focused to assure the public is accurately informed about the health effects of the new products and to assess the relative toxicity of all products offers a reasonable possibility of achieving a net gain in health from use of PREPs.

While fully addressing research needs will take years of concerted effort, immediate actions also are required to successfully achieve a goal of harm reduction. Today, there is little public authority over tobacco products of any type. Thus, the committee concluded that in order to obtain the best available scientific evaluation of current and emerging PREPs, and to provide the best advice on these products to the public, some national authority over PREPs is needed. Only a comprehensive program of surveillance and regulation focused to assure the public is accurately informed about the health effects of the new products and to assess the relative toxicity of all products offers a reasonable possibility of achieving a net gain in health from use of PREPs.

Surveillance

Toward this end, the committee recommended development of a national surveillance system to assess the relative contribution of PREPs to the health of the public. This system would collect information on a range of elements necessary to understand the population impact of tobacco products and PREPs, including consumer attitudes and beliefs, product characteristics and usage patterns, marketing messages, rates of people who start or quit using tobacco products, and the prevalence of major smoking-related diseases, population level biomarkers indicating actual degree of tobacco or tobacco smoke exposure, among other information. The tobacco industry would be required to provide data on the constituents of tobacco products as well as on product distribution and sales.

Implementation

In order to best implement the scientific and policy recommendations made, the committee further recommended development of a national regulatory system for all modified tobacco products with risk-reduction or exposure-reduction claims, explicit or implicit, and for any other products offered to the public to promote reduction or cessation of tobacco use. For this purpose, the regulatory framework outlined is narrow and focused exclusively on evidence supporting claims and any necessary powers required to assess PREPs, pharmaceutical or tobacco-related. This network would build on the foundation of existing food and drug laws, with adaptations to take into account the unique history and toxicity of tobacco products.

In sum, the committee determined that it is both feasible and desirable to implement a comprehensive, scientifically based program that promotes and assesses the use of PREPs. Such a system must be carefully implemented and must incorporate the following features:

- Manufacturers have incentive to develop and market products that reduce exposure to tobacco toxicants and that have a reasonable prospect of reducing the risk of tobacco-related disease.
- Consumers are accurately informed of all of the known, unknown, likely, and potential consequences of using these products.

- Promotion, advertising, and labeling of these products are firmly regulated to prevent false or misleading claims.
- Health effects of using PREPs are monitored on a continuing basis.
- Basic, clinical, and epidemiological research is conducted to establish the potential use of PREPs for reducing risks for disease in individuals and for reducing harm to the population as a whole.
- Harm reduction is implemented as a component of a comprehensive national tobacco control program that emphasizes abstinence-oriented prevention and treatment.

As outlined here, a comprehensive approach that utilizes scientific research, surveillance, and regulatory tools is necessary for the realization of the potential individual and societal benefits of tobacco harm reduction.

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For More Information . . .

Copies of *Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction* are available for sale from the National Academy Press; call (800) 624-6242 or (202) 334-3313 (in the Washington metropolitan area), or visit the NAP home page at www.nap.edu. The full text of the report is available on line at <http://books.nap.edu/catalog/10030.html>

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